REMARKS

A. Objection to the Declaration

The Examiner objected to the declaration because it incorrectly claims to priority to Provisional Application No. 60/097,864, rather than Provisional Application No. 60/097,846. Applicant will submit a substitute declaration correcting this typographical error.

B. Rejection of Claim 2 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 2 as indefinite, asserting that "the term 'substantial' muscle weakness has not been defined", and that, thus, "said weakness might range from the undetectable to total paralysis." Applicant has amended claim 2 to remove the term "substantial", and thus submits that claim 2 is now allowable. This amendment is made for the purpose of expediting prosecution and without prejudice to applicant's right to pursue the original claim in a continuation application.

C. Rejection of Claim 4 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 4 as indefinite, asserting that while the specification refers to "units", "mouse units", and "LD50 units", the term "'units' has not been defined." These terms are used identically in the specification to refer to units of a chemodenervating pharmaceutical measured using the mouse LD50 assay that is well-known by those of ordinary skill in the relevant art: "The botulinum unit is defined as that quantity of botulinum toxin capable of killing 50% of a population of Swiss Webster mice." (6th paragraph of "Background of Invention" section of specification.) With this

assay, a single unit of chemodenervating pharmaceutical is defined as that amount which leads to the death of half the mice on average that have been treated with that amount.

Applicant has amended claim 4 to recite "botulinum units", solely for the purpose of clarifying that the claim term "units" refers to the units defined in the specification, and referred to in the specification identically as "botulinum units", "mouse units", and "LD50 units". As disclosed in the specification, these terms are synonyms, and thus this amendment does not narrow the scope of the claim.

D. Rejection of Claims 17-23 Under 35 U.S.C. § 112, ¶ 1 for Lack of Written Description

The Examiner rejected claims 17-23 for lack of sufficient written description in the specification to reasonably convey to one of ordinary skill in the relevant art that the inventor had possession of the claimed invention at the time of filing.

With respect to claims 17, 19, and 21-23, the Examiner failed to find support in the specification for "a method for treating neurogenic inflammation" and "at least one neurogenic inflammatory mediator". Applicant believes that support for these aspects of the invention are found amply throughout the specification. For example:

"[C]hemodenervative pharmaceuticals such as botulinum toxin...are effective anti-inflammatory agents." (Second paragraph of "Summary of Invention".)

"[A]nti-inflammatory action is explained by resultant blockage of mast cell and nerve cell release of histamine and other preformed mediators which result in vascular dialation, increased permeability, altered sensory experience, edema and erythema." (Third paragraph of "Summary of Invention".)

"The subject anti-inflammatory agent's unique property relates to the suppression of the component for the inflammatory response which occurs rapidly, and which is mediated by neural reflex mechanisms." (Sixth paragraph of "Summary of Invention".)

"[I]nflammation in torticollis in peripheral tissues may be neurogenically mediated." (Third paragraph of "Spasmodic Torticollis".)

Indeed, one of ordinary skill in the art, when reading the specification as a whole, would understand that the invention encompasses the treatment of neurogenic inflammation and the antagonism of at least one neurogenic mediator. All of the extensive discussion throughout the specification of mast cell and nerve cell release of "preformed mediators" and the blockage of such release by chemodenervating pharmaceuticals, such as botulinum toxin, would be clearly understood by one of ordinary skill in the art as referring to neurogenic inflammation and neurogenic mediators, and as indicating that the inventor had the invention as claimed in claims 17, 19, and 21-23 in his possession at the time of filing.

One of ordinary skill in the art would have understood at the time of filing that the disclosures in the specification enumerated above refer specifically to neurogenic inflammation. That this is so can be seen by looking

at the specification of U.S. Patent No. 6,063,768 to First, entitled "Application of Botulinum Toxin to the Management of Neurogenic Inflammatory Disorders" ("First"). First explains in some detail with numerous references to the scientific literature how the term "neurogenic inflammation" would be understood by one of ordinary skill in the art:

> The contribution of the nervous system in inflammation has been recognized since Lewis (1932, 1936) proposed that the characteristic wheal and flare responses are mediated by the release of pro-inflammatory substances (described in detail below) from peripheral nerve endings of nociceptive afferent pathways.
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> * * *
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> The responses mediated by the peptides and transmitters released from sensory nerves include vasodilation (via cGRP release), and increased vascular permeability (via SP release) (Jancso et al., 1967; Lembeck and Holzer, 1979; Saria, 1984; McDonald et al., 1996; Anichini et al., 1997; Strittmatter et al., 1997; Carlson et al., 1996; Lundeberg et al., 1996). In addition, the activation of the immune system intiates the attraction of white cells, activation of phagocytic function of neutrophils and macrophages, stimulation of the increased production and release of inflammatory mediators from these cells and the degranulation of mast cells and local release of histamine (Helme and Andrews, 1979; Siato et al., 1986; Payan et al., 1984; Bar-Shavitz et al., 1980; Hartung et al., 1986; Johnson and Erdos, 1973; Naukkarinen et al., 1996). * * * The result of this neuroendocrine cascade of events has been termed, neurogenic inflammation (Jancso, 1967) and works as a central network modulating the events between the immune, nervous and endocrine systems.

(First, Col. 2, lines 19-57).

In characterizing the treatment of neurogenic inflammation with botulinum toxins, First states that "cells that release neuropeptides and other mediators, activators or promoters of inflammation such as sensory and autonomic neurons and other secretory cells play a role in inflammation" and that "botulinum toxins block the actions of these mediators" (First, Col. 1, lines 24-29). Likewise, the instant application discloses that "this new bioeffect of anti-inflammatory action is explained by the resultant blockage of mast and nerve cell release of histamine and other preformed mediators which result in vascular dialation *[sic]*, increased permeability, altered sensory experience, edema and erythema", and that "it is thus a finding of this invention that inflammation is inhibited by administration of the subject chemodenervative agent" (Fourth paragraph of "Summary of Invention").

Consistent with the characterization of neurogenic inflammation of First and of the instant application, Sann et al. (1996; enclosed herewith) discloses that "neurogenic inflammation appears to be mediated by a local release of sensory neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP)", and that "[sensory] nerves are capable of releasing neuropeptides such as SP, neurokinin A [NKA] and CGRP from their peripheral endings which, in turn, provoke neurogenic inflammatory responses".

McDonald et al. (1996, enclosed herewith) also describes how one of ordinary skill in the art would understand the term "neurogenic inflammation" at the time of filing of the instant application:

> The term neurogenic inflammation describes the increase in vascular permeability produced by substances released from sensory nerves.
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> * * *
>
> Neurogenic inflammation is mediated by substance P and perhaps other peptides released from unmyelinated sensory axons.
>
> * * *
>
> Substance P...appears to be the main active mediator, akthough other tachykinins, calcitonin gene-related peptide, and perhaps other peptides may also participate.
>
> * * *
>
> [P]lasma leakage produced by histamine and bradykinin is partly dependent on sensory nerves.
>
> * * *
>
> Neurogenic inflammation...has been identified in the dura, conjunctiva, eye lid, middle ear, oral mucosa, dental pulp, salivary gland ducts, esophagus, biliary system, anal mucosa, ureter, urinary bladder, skin, joints, nose, larynx, trachea, and bronchi[.]
>
> * * *
>
> [E]ach organ exhibits its own unique collection of effects of mediators released from sensory nerves.

The instant application discloses that "this new bioeffect of anti-inflammatory action is explained by the resultant blockage of mast and nerve cell release of histamine and other preformed mediators which result in vascular dilation, increased permeability, altered sensory experience, edema and erythema" (Fourth paragraph of "Summary of Invention"). In the third paragraph of "Mast Cells", the applicant cites a paper entitled "Histamine and

Tumor Necrosis Factor-alpha Production From Purified Rat Brain Mast Cells Mediated by Substance P", thus disclosing the role played by substance P in triggering neurogenic inflammation, as described in the references cited above. It should thus be clear that the disclosure of the instant application would be understood by one of ordinary skill in the art to indicate that the applicant had in his possession at the time of filing the invention as particularly claimed in claims 17-23, because the application has clear written description of applicant's invention that chemodenervative pharmaceuticals such as botulinum toxins may be used to successfully treat neurogenic inflammation.

Regarding claim 19, the Examiner failed to find support in the specification for "substance-P, calcitonin gene-related peptide, vasoactive intestinal peptide, interleukin-1, interleukin-2, nitric oxide, 5-hydroxytryptamine, tumor necrosis factor, and nerve growth factor". In the first paragraph of the "Background of the Invention" section of the specification, applicant explicitly refers to inflammation as involving "complement, arachidonic acid metabolites such as prostaglandin and leukotrienes, cytokines, preformed mediators such as serotonin and histamine, and enzymes." One of ordinary skill in the art would understand that the term cytokine is defined in the art as referring to interleukin-1, interleukin-2, and tumor necrosis factor, and that 5-hydroxytryptamine is a synonym for serotonin. In the first paragraph of the "Summary of the Invention", applicant explicitly states that "low dosages of the subject chemodenervative agent reduces histamine release and releases of other preformed mediators

associated with mast cell degranulation." In the second and third paragraphs of the "Mast Cells" section of the specification, applicant explicitly refers to "preformed mediators such as histamine, newly formed mediators such as leukotrienes and prostaglandins, cytokines, including interleukin-5, interleukin-8, kininogenase, and platelet activating factor", as well as "tumor necrosis factor alpha" and "substance P". Thus, support for the terms "substance P", "interleukins", "tumor necrosis factor", and "serotonin" are explicitly found in the specification. With regard to the other terms recited in claim 19, one of ordinary skill in the relevant art would clearly understand that applicant's explicit references in the specification to "preformed mediators", "cytokines", and "newly-formed mediators" encompasses all of the specific neurogenic inflammatory mediators enumerated in claim 19, and thus indicates that applicant was in possession at the time of filing of the invention in every particular as claimed in claim 19.

For claim 22, the Examiner failed to find support in the specification for "wherein the neurogenic inflammation is caused by gout". In the second paragraph of the section of the specification entitled "Rheumatoid Arthritis", applicant refers to the invention as offering "a means of localized application of an anti-inflammatory agent which is injected directly into joints...which creates an effect on the rapid inflammatory response and peripheral neural elements governing the inflammatory response." In other words, it is within the scope of the invention as disclosed in the specification to treat neurogenic inflammation of the joints. It is well understood by those of skill in the art that gout is a

disease that is most fundamentally characterized by inflammatory response in the joints. Thus, one of ordinary skill in the relevant art would clearly conclude from applicant's statements in the specification regarding treatment of joint inflammation with chemodenervating pharmaceuticals that applicant was in possession at the time of filing of the invention as claimed in claim 22—including specifically the treatment of neurogenic inflammation caused by gout.

Regarding claim 23, the Examiner failed to find support in the specification for "treating the neurogenic inflammation by inhibiting histamine". Applicant discloses in numerous places in the specification that it is within the scope of the invention to reduce inflammation by inhibiting histamine. For example, in the first paragraph of the "Summary of the Invention", applicant explicitly states that "low dosages of the subject chemodenervative agent *reduces histamine releases*" (emphasis added). Claim 15 as originally filed recites "botulinum toxin immunotypes which block mast cell release of histamine". Furthermore, in the various examples disclosed later in the specification, such as successful treatment with chemodenervative pharmaceuticals of cholinergic urticaria, treatment of blepharoconjunctivitis, etc., it is well known in the relevant art that those disorders are always associated with increased histamine activity in the affected tissues, and that increased histamine activity is a major cause of the inflammation. It would thus be clear to one of skill in the relevant art that applicant, at the time of

filing, was in possession of the invention as claimed in claim 23—including the treatment of neurogenic inflammation by inhibiting histamine.

E. Rejection of Claims 2-5 Under 35 U.S.C. § 112, ¶ 1 for Lack of Enablement

The Examiner rejected claims 2-5 on the ground that the specification disclosure is insufficient to enable one of ordinary skill in the art to practice the invention as broadly as claimed without undue experimentation.

The Examiner failed to find support in the specification for a method for reducing inflammation without causing substantial muscle weakness and with an effective dose of botulinum toxin of less than 2.5 units. The specification provides a number of working examples of treating inflammation with a chemodenervative pharmaceutical, such as botulinum toxin, without causing muscle weakness, and with doses within the claimed range. For example, in the fourth paragraph of the section of the specification entitled "Spasmodic Torticollis", applicant discloses a working example wherein "botulinum toxin injected into red areas noted to be painful and thermally active in accordance with the subject invention has been demonstrated to block the erythema, pain, increased tenderness, and heat loss within the area", and that "minimum doses [for achieving this effect] range between 0.6 units to 15 units and are *far lower than that required to produce regional weakness*" (emphasis added). As explained throughout the specification, and as well-understood by physicians for centuries, redness (erythema), pain, increased tenderness, and heat loss are some of the cardinal defining characteristics of inflammation. As another example, in the third paragraph of the section of the specification entitled

"Conjunctivitis", applicant discloses as a working example "inject[ion] with .675 mouse units of botulinum toxin". Thus, one of ordinary skill in the art finds ample support in the specification for successfully treating inflammation with a chemodenervating agent, such as botulinum toxin, with a dose less than 2.5 units and without causing muscle weakness.

The Examiner also failed to find support in the specification for a method of reducing inflammation comprising administering botulinum toxins B-G. In the seventh paragraph of the "Background of the Invention", applicant discloses that "botulinum is known to exist as immunotypes A-G", and that "each immunotype has been associated with varying durations of action and chemodenervating potency per LD 50 unit, as described by Borodic, G.E., Pearce, L.B., New Concepts in Botulinum toxin Therapy, Drug Safety 11(3): 145-152, 1994." In the fifth paragraph of "Mast Cells", the applicant discloses that "[a]lthough botulinum toxin type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin type B-G may be substituted based on demonstrated anti-inflammatory efficacy". Physicians skilled in the art titrate botulinum toxin doses upward from lower levels as individual variation in botulinum toxin dose response does occurs from patient to patient. This titration is not undue experimentation—rather, it is within the scope of ordinary medical practice in the use of pharmaceutical agents to treat human patients.

F. Rejection of Claims 1, 5-6, and 17-23 under 35 U.S.C. § 102(e) as Anticipated by U.S. Patent No. 6,063,768

The Examiner has rejected claims 1, 5-6, and 17-23 as being anticipated by U.S. Patent No. 6,063,768. (Sec. 13.) Applicant notes that he filed a Request to Declare Interference with the '768 patent on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared with respect to these claims in accordance with the applicable rules and standards.

G. Rejection of Claims 1, 5-8, 10-12, and 17-23 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,063,768 in View of the Merck Manual

The Examiner rejected claims 1, 5-8, 10-12, and 17-23 as *prima facie* obvious over the '768 patent and the Merck Manual. Applicant notes that he filed a Request to Declare Interference with the '768 patent on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared with respect to these claims in accordance with the applicable rules and standards.

In light of the foregoing, as well as the content of the telephonic interview held with the Examiner on March 18, 2002, applicant submits that pending claims 2, 3, and 4 in this application are in condition for allowance, and a favorable action by the Examiner with respect to those claims is respectfully requested. Applicant further submits that claims 1, 5-8, 10-12, and 17-23 are in condition for allowance in every respect except with regard to the rejections over U.S. Patent No. 6,063,768. As explained above, applicant has filed a Request to Declare Interference between the present application and the '768 patent.

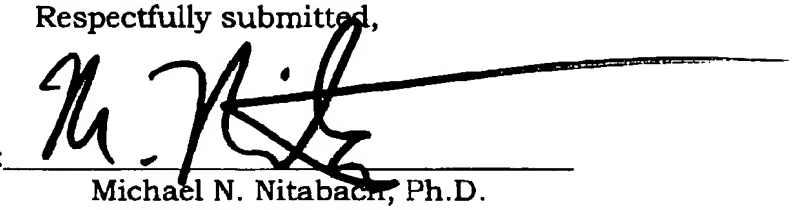
Applicant continues to be appreciative of the Examiner's prompt consideration of the claims and arguments presented. Applicant reiterates his respectful request that examination of the instant application continue to be with "special dispatch" under 37 C.F.R. § 1.607(a)(6).

If the Examiner is of the opinion that it would assist in placing claims 2, 3, and 4 in condition for allowance, and claims 1, 5-8, 10-12, and 17-23 in condition for allowance other than with regard to the prior art rejections over the '768 patent, or otherwise expedite prosecution, the applicant invites the Examiner to contact his counsel by telephone at the number listed below.

No extension of time is believed necessary for this filing. However, the Commissioner is hereby authorized to charge any extension of time or other fees which may be required for this paper to Deposit Account Number 13-3250, Order No. 33677-00000.

Respectfully submitted,

Dated: March 26, 2002

By: 

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